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Abstract #TPS4217

A randomized phase 2 study of casdozokitug, an IL-27 targeting antibody, in combination with toripalimab plus bevacizumab in patients with unresectable and/or locally advanced or metastatic hepatocellular carcinoma

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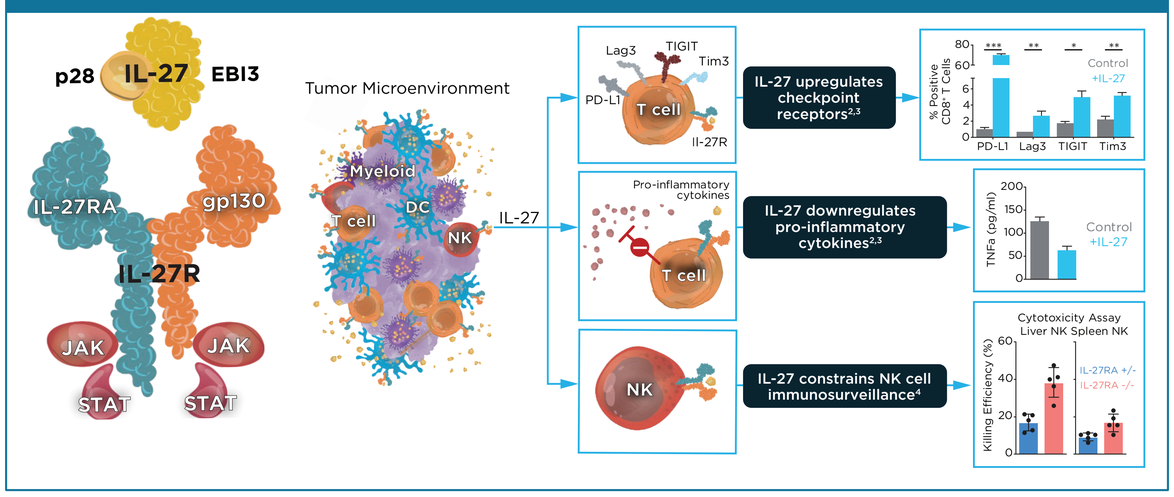
BACKGROUND

- IL-27 is a member of the IL-12/IL-23 cytokine family comprised of IL-27p28 and EBI3 subunits. It is an immunoregulatory cytokine expressed by myeloid cells, including macrophages and dendritic cells, and dampens T and NK cell effector function.
- IL-27 is highly expressed by tumor-associated macrophages (TAM) in several cancers, including liver (hepatocellular carcinoma [HCC], highest expression of IL-27p28 mRNA), renal cell carcinoma (RCC), and lung (non-small cell lung cancer [NSCLC]), and suppresses antitumor immune responses.
- Casdozokitug (or casdozo; CHS-388; formerly SRF388) is a first-in-class high affinity IL-27 antagonistic antibody, which promotes immune activation and stimulates antitumor response.
- Inhibiting IL-27 by genetic deletion or inhibiting the cytokine with an antagonistic antibody resulted in antitumor activity in 3 HCC models: Hep1-6, NASH induced model and carcinogen induced model.

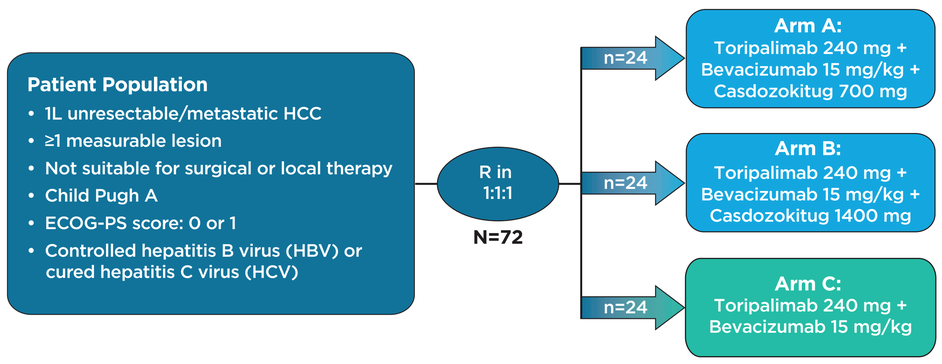
IL-27 Inhibits T and NK Cell-Driven Antitumor Response in the Tumor Microenvironment



- In a phase 1 study (NCT04374877), casdozokitug demonstrated a favorable safety profile and antitumor activity per RECIST in indications known to have high levels of IL-27 pathway activation (NSCLC and RCC [monotherapy] and HCC [in combination with PD-1 blockade]).[1]
- A phase 2 study (NCT05359861) of casdozokitug + atezolizumab + bevacizumab in locally advanced or metastatic HCC showed an acceptable safety profile and antitumor activity (overall response rate [ORR] 38% and median progression-free survival [mPFS] 8.1 months [mo]).[2]
  - The triplet therapy resulted in a complete response (CR) rate of 17.2%,[2] which is higher than previously reported phase 3 HCC studies with CR rates of 3-8% (IMbrave150 and HIMALAYA).[3,4]
- A phase 3 study (NCT04723004) of toripalimab + bevacizumab as first-line treatment of advanced HCC demonstrated significant improvements in efficacy compared to sorafenib (ORR 25.3% vs 6.1% [CR 0% vs 0%], mPFS 5.8 mo vs 4.0 mo, median overall survival [mOS] 20.0 mo vs 14.5 mo).[5] This study supported approval in China.
- The current study (CHS-388-202 [NCT06679985]) will evaluate the efficacy, safety, and biomarkers of toripalimab + bevacizumab ± casdozokitug and optimize the dose for casdozokitug in combination with toripalimab + bevacizumab as first-line treatment for patients with unresectable and/or locally advanced/metastatic HCC using two pharamcologically active doses.

STUDY DESIGN

- CHS-388-202 is a phase 2, open-label, randomized study.
- This study will enroll up to 72 patients randomized (1:1:1) to 1 of 3 treatment arms (intravenously [IV] every 3 weeks [Q3W]):



Two Stratification Factors:

- **Geographic region: Asia, excluding Japan, versus the rest of the world**
- **Macrovascular invasion or extrahepatic spread of disease (presence vs. absence)**

1L, first-line; ECOG PS, Eastern Cooperative Oncology Group Performance Status; kg, kilogram; mg, milligram; R, randomized.

REFERENCES: **1.** Marron TU, et al. *Ann Oncol*. 2023;20(suppl_1): 100589-100589. 10.1016/iotech/iotech100589. **2.** Li et al. *J Clin Oncol*. 2025;43(suppl 4):605. **3.** Cheng, et al. *J Hepatol*. 2022;76,862-873. **4.** Abou-Alfa, et al. *NEJM Evid*. 2022; 1, EVIDoa2100070. **5.** Yinghong S, et al. Oral presentation at: CSCO 2024; September 27, 2024; Xiamen, China.

DISCLOSURE: Study sponsored by Coherus.

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KEY OUTCOME MEASURES

PRIMARY

- Safety as measured by incidence and severity of treatment-emergent adverse events (TEAEs), clinical laboratory values, electrocardiograms, vital signs, and physical examination
- Efficacy as measured by ORR by investigator review (RECIST v1.1)

SECONDARY

- ORR by investigator review (HCC mRECIST)
- Duration of response by investigator review (RECIST v1.1 and HCC mRECIST)
- PFS by investigator review (RECIST v1.1 and HCC mRECIST)
- Disease control rate by investigator review (RECIST v1.1 and HCC mRECIST)
- OS
- Concentration-time data and pharmacokinetic (PK) parameters including maximum concentration (C_{max}), minimum concentration (C_{min}), time to C_{max} (T_{max}), clearance, half-life, and trough levels of casdozokitug and toripalimab

ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

- ≥ 18 years of age
- Unresectable locally advanced or metastatic HCC with diagnosis confirmed by histology/cytology or clinically by AASLD criteria in cirrhotic participants
- Disease that is not amenable to curative surgical and/or locoregional therapies or progressive disease after surgical and/or locoregional therapies
- ≥1 measurable lesion (per RECIST v1.1) that is untreated
- ECOG PS of 0 or 1
- Laboratory values indicative of adequate organ function
- Child-Pugh Class A
- Controlled HBV or Cured HCV
- Baseline tumor tissue sample is mandatory; an archival tumor tissue is acceptable

KEY EXCLUSION CRITERIA

- Has received prior systemic therapy for HCC
- Has received an anti-IL-27 antibody or anti-IL-27-targeted therapy
- Has known fibrolamellar HCC histology, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Has moderate or severe ascites
- Has uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
- Has a history of or current hepatic encephalopathy
- Has untreated or incompletely treated varices with bleeding or high risk for bleeding
- Locoregional therapy to HCC within 28 days prior to initiation of study treatment or non-recovery from complications due to the procedure
- Symptomatic or untreated brain metastases or leptomeningeal carcinomatosis
- Has received a prior allogeneic hematopoietic cell transplant or solid tumor organ transplant
- Active or history of autoimmune disease or immune deficiency
- History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, interstitial pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Has active tuberculosis

STATISTICAL AND DATA ANALYSIS

- **Efficacy analyses:**
  - **Primary efficacy endpoint analysis:** ORR (confirmed PR + CR) will be based on RECIST v1.1 as assessed by the Investigators. For the analysis of ORR, 95% CI will be calculated using the Clopper-Pearson method.
  - **Secondary efficacy endpoints analyses:** All tumor-based endpoints will be assessed by the Investigators according to RECIST v1.1 and HCC mRECIST. For analysis of DCR, 95% CI will be calculated using the Clopper-Pearson method. If the number of participants is higher than 10 per treatment arm, median time and 95% CI for the median time will be calculated using the Kaplan-Meier method for analysis of DoR, PFS, and OS.
- **Safety analyses:** TEAEs will be summarized by treatment arm, frequency, and by MedDRA SOC and PT. Separate tabulations will also be produced for TEAEs assessed as related to study drug, TEAEs that led to treatment discontinuation, TEAEs that led to death, AESI, and TEAEs grade ≥ 3 in severity. TESAEs and TESAEs related to study drug will also be tabulated.
- **Pharmacokinetic analyses:** Blood samples will be analyzed for casdozokitug and toripalimab concentrations using validated methods. PK parameters based on the actual sample collection times will be calculated using standard noncompartmental methods. PK parameters for casdozokitug and toripalimab will be summarized descriptively by the treatment arm.

ADDITIONAL STUDY INFORMATION

- A safety run-in evaluation will be conducted after the first ~6 patients are enrolled in arms A and B, with ≥3 from each arm completing 1 cycle of treatment.
- Patients will remain on study treatment for ≤2 years or until documented disease progression or unacceptable toxicity.
- Enrollment in the United States (US) is ongoing and is expected to expand outside of the US to Canada and countries in Europe and Asia soon.